Thoughts?

Bruce

From: Lisa Graver
Sent: Wednesday, November 11, 2009 11:01 AM
To: Bruce Sullivan
Subject: FW: Oxycodone ER launch

Attorney-Client

Lisa Graver
Vice President-Intellectual Property

actavis
creating value in pharmaceuticals

Actavis
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Elizabeth , NJ 07202 United States w www.actavis.com
Internal VoIP number ℓ 1202510

From: Michael Perfetto
Sent: Tuesday, November 10, 2009 12:50 PM
To: Lisa Graver; Doug Boothe
Cc: Jinping McCormick; Bob Miranda; Chris Gordon
Subject: FW: Oxycodone ER launch

Attorney-Client

PLAINTIFFS TRIAL EXHIBIT
P-01092_00001

tx

Michael Perfetto
VP, Sales and Marketing

Actavis
60 Columbia Rd. Bldg B t 908-868-9778 @ mperfetto@actavis.com
Morristown , NJ 07960 United States f 607-724-0322 w www.actavis.com
Internal VoIP number

From: Jinping McCormick
Sent: Tuesday, November 10, 2009 12:32 PM
To: Lisa Pehlke; Michael Berryman; Michael Dorsey; Michael Perfetto; Nancy Baran; Steve Cohen; Thad Demos; Andrea Johnson; Bob Miranda; Chris Gordon; John Reed; Soojung Chung; Violet Wojtulewicz
Cc: David Myers; Karen Stoedter
Subject: Oxycodone ER launch

All,

Enclosed please find the following information for Oxycodone ER launch:

- Sell sheet including PI – can be sent to customers. Hard copies are being printed as we speak.
- Product profile sheet
- Container labels
- PI
- HDMA forms

Please note the official name on the label is Oxycodone HCl **Controlled-release** Tablets. This tablets color and imprints are exactly the same as the brand.

Please take a look at the HDMA forms, pricing and let me know if anything needs to be corrected.

Jinping

HDMA Standard Product Information — Pharmaceutical Products

☒ New Item ☐ Promotion/Deal ☐ Open Stock ☐ Post Launch Change

Date: Nov 24, 2009

PRODUCT INFORMATION

Manufacturer/Broker Name: Actavis Totowa LLC Number: 52152

Product Name: Oxycodone controlled release tablets 80mg

Product ID Number:

☒ NDC 52152-411-02 ☒ UPC/GTIN # 3 52152-411-02 0

Description: Round, unscored, green-colored, convex tablets imprinted with OC on one side and 80 on the other

Address: 990 Riverview Drive

City, State, Zip: Totowa, NJ 07512

Key Contact: Jinping McCormick Fax:

Phone Number: 888-925-2342 Ext:

Phone Number: Ext:

Is the Product? ☒ Direct Ship Item ☐ Drop Ship Item

Is the Product a Controlled Drug? ☒ Yes ☐ No

If Yes, Schedule Number: C II

Is this ARCOS reportable? ☐ Yes ☐ No

Is this Product a Legend Device? ☐ Yes ☒ No

Country of Origin: USA

Harmonization Code Number for International Shipping:

Is this product a Hazardous Material or Cytotoxic Agent?

☐ Yes ☒ No If yes, provide additional information on page 2.

Attach copy of Material Safety Data Sheet (MSDS)

Attach Package Insert

SPECIAL HANDLING AND STORAGE REQUIREMENTS

a. Temperature – Indicate the normal temperature range for this product.

I.	Controlled Room Temperature (68° – 77° F)	☒
II.	Room Temperature (59° – 86° F)	☐
III.	Excessive Heat (>104° F)	☐
IV.	Cool (46° – 59° F)	☐
V.	Refrigerated (36° – 46° F)	☐
VI.	Frozen (-4° – 14° F)	☐
VII.	No Requirement	☐

b. Are temperature excursions permitted/allowed for product? ☒ Yes ☐ No

If Yes, provide the temperature range and hours duration:

59 -86F and

c. Are there additional storage and shipping requirements? ☐ Yes ☒ No

If yes, please provide on page 2.

ADDITIONAL PRODUCT INFORMATION

Is there a minimum order quantity?

If yes, ☐ Case ☐ Carton ☒ Item

Number of Pieces? 48

Shelf Life: 35 Months

Whsl. Code #:

Fineline Code:

Is Item? ☐ Unit Dose ☐ Unit of Use

If Unit Dose, is item bar coded to unit dose for Hospital tracking purposes?

☐ Yes ☐ No

Will handling data change in the first:

6 months? ☐ Yes

9 months? ☐ Yes

12 months? ☐ Yes

Unknown? ☐ Yes

ITEM AND PACKING INFORMATION

Size/Strength /Form	Unit Of Sale	UPC Code	Mstr. Shpr.	Inner Case Pk	Wght. Lbs.	Cube	Case Dimensions	Item Dimensions	Pallet Dimensions	# Cases/ Pallet
100/80mg/ CR Tablets	☒ Bottle ☐ Box ☐ Glass jar ☐ Ampule ☐ Other	Case:	48		Case: 4.25 lb	0.37 cu ft	Depth: 11.81"	Depth: 1.83"	Depth: 40"	100
		Carton:			Carton:		Height: 7.38"	Height: 3.28"	Height:	
		Item: 3 5215241102 0			Item: 1.34 oz		Width: 7.31"	Width: 1.63"	Width: 48"	

For Generic Drug Products:

I. Orange Book Rating: AB

II. Product Color: green

III. Brand Name Equivalent: OxyContinr

IV. Generic Name For Brand: Oxycodone CR Tablet

COST INFORMATION

	Regular Cost ($)	Purchase Allowance ☐ OI ☐ BB $	Purchase Allowance %	Distribution Allowance ☐ OI ☐ BB $	Distribution Allowance %	Invoice Cost ($)	Net Cost ($)	Mfr's AWP	Avg Retl Price ($)	SRP ($)	Excise Tax
DZ											
EA						$974.75		1170.17			
PPK											

This offer is made on a proportionally equal basis to all sellers' accounts completive with customer. **Signature:**

Revised 02/21/06

Item Description: Oxycodone CR Tablets **Manufacturer:** Actavis Totowa LLC

If additional information is necessary, provide on right of page or as attachment.

HAZARDOUS MATERIAL INFORMATION

Is this product:

- a) Cytotoxic? ☐ Yes ☒ No
- b) Carcinogen? ☐ Yes ☒ No
- c) Inhalation Hazard? ☐ Yes ☒ No
- d) Contact Hazard? ☐ Yes ☒ No

Is this item considered a carcinogen? ☐ Yes ☒ No

Is this item an aerosol requiring special storage? ☐ Yes ☒ No

Does this product require special clean-up instructions? ☐ Yes ☒ No

If yes, attach MSDS with special instructions.

Department of Transportation (DOT) I.D. Number: _____

Hazard Class/ORM Code: _____

OSHA/DOT CHEMICAL STORAGE CLASS

Please check appropriate Class(s) for this product.

☒ ORGANIC	☐ ANTINEOPLASTIC
☐ INORGANIC	☐ STEROID/ANDROGEN
☐ CORROSIVE/OXIDIZER	☐ ESSENTIAL CHEMICAL
☐ AEROSOL	☐ PRECURSOR CHEMICAL (Describe below)
☐ AEROSOL CLASS	☐ MAXIMUM QTY LEVEL

Is the product restricted for air shipping?

- ☐ Passenger
- ☐ Cargo
- ☐ Passenger & Cargo

Precursor Chemical:			Size/Strength
Ephedrine	☐ Yes	☒ No	_____
Pseudoephedrine	☐ Yes	☒ No	_____
Phenylpropanolamine	☐ Yes	☒ No	_____

ADDITIONAL STORAGE AND SHIPPING REQUIREMENTS

Is this product to be shipped to customers on ice? ☐ Yes ☒ No

Is this product to be shipped to customers on dry ice? ☐ Yes ☒ No

Does this product require refrigerated truck for transport? ☐ Yes ☒ No

Is this Product State Regulated? ☐ Yes ☐ No

If yes, list states on the right or as an attachment.

Are there special returns requirements? ☐ Yes ☒ No

If yes, provide requirements in the space to the right or as attachment.

ADDITIONAL INFORMATION AS NECESSARY

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Oxycodone Hydrochloride Controlled-Release Tablets CII

National Brand Name: OxyContin® Tablets (RX) OTC

Brand Manufacturer: Purdue Pharma L.P.

Therapeutic Rating: Compared to OxyContin® Tablets

Product Description: Active Ingredient: Oxycodone Hydrochloride

10 mg: Round, unscored, white-colored, convex tablets imprinted with OC on one side and 10 on the other.

20 mg: Round, unscored, pink-colored, convex tablets imprinted with OC on one side and 20 on the other.

40 mg: Round, unscored, yellow-colored, convex tablets imprinted with OC on one side and 40 on the other.

80 mg: Round, unscored, green-colored, convex tablets imprinted with OC on one side and 80 on the other.

Label: **Actavis**

Packaging Information:

	10 mg 100s	20 mg 100s	40 mg 100s	80 mg 100s
NDC Number:	52152-408-02	52152-409-02	52152-410-02	52152-411-02
UPC Number:	3 52152-408-02 0	3 52152-409-02 7	3 52152-410-02 3	3 52152-411-02 0
Case Quantity:	48 Bottles	48 Bottles	48 Bottles	48 Bottles
Case Dimensions (LxWxH):	11.81" x 7.31" x 7.38"	11.81" x 7.31" x 7.38"	11.81" x 7.31" x 7.38"	11.81" x 7.31" x 7.38"
Case Cube:	0.37 ft	0.37 ft	0.37 ft	0.37 ft
Case Weight:	4.25 lb	4.25 lb	4.25 lb	4.25 lb
Bottle Dimensions (HxDxW):	3.28" x 1.83" x 1.63"	3.28" x 1.83" x 1.63"	3.28" x 1.83" x 1.63"	3.28" x 1.83" x 1.63"
Bottle Weight:	1.34 oz	1.34 oz	1.34 oz	1.34 oz

* OxyContin® is a registered trademark of Purdue Pharma L.P.

A253 Rev 10/2009

Each Controlled-Release Tablet Contains:
Oxycodone Hydrochloride, USP ..... 10 mg

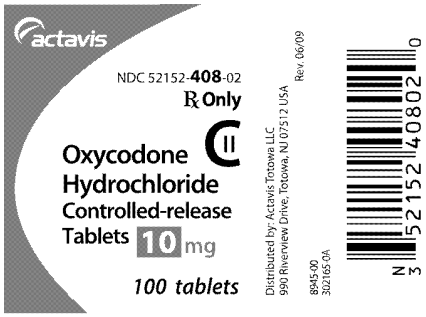
Usual Dosage: See package outsert for full prescribing information.

Swallow tablets whole. Do not crush, break, or chew.

Dispense in a tight, light-resistant container.

Store at 20°-25°C (68°-77°F); with excursions permitted between 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

U.S. Patent Nos.: 5,508,042; 7,129,248



Distributed by: Actavis Totowa LLC
990 Riverview Drive, Totowa, NJ 07512 USA

Rev. 06/09

8945-90
302165 0A

Each Controlled-Release Tablet Contains:
Oxycodone Hydrochloride, USP ..... 20 mg

Usual Dosage: See package outsert for full prescribing information.

Swallow tablets whole. Do not crush, break, or chew.

Dispense in a tight, light-resistant container.

Store at 20°-25°C (68°-77°F); with excursions permitted between 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

U.S. Patent Nos.: 5,508,042; 7,129,248

actavis

NDC 52152-**409**-02

℞ **Only**

Oxycodone Hydrochloride Controlled-release Tablets 20 mg

CII

100 tablets

Distributed by: Actavis Totowa LLC
990 Riverview Drive, Totowa, NJ 07512 USA

Rev. 06/09

8946-00
302166-0A

Each Controlled-Release Tablet Contains:
Oxycodone Hydrochloride, USP ..... 40 mg

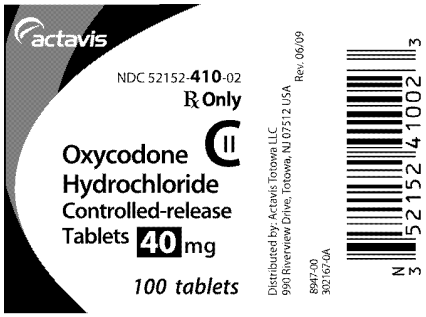
Usual Dosage: See package outsert for full prescribing information.

Swallow tablets whole. Do not crush, break, or chew.

Dispense in a tight, light-resistant container.

Store at 20°-25°C (68°-77°F); with excursions permitted between 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

U.S. Patent Nos.: 5,508,042; 7,129,248



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990 Riverview Drive, Totowa, NJ 07512 USA

Rev. 06/09

8947-00
302167-0A

N 3 52152 41002 3

Each Controlled-Release Tablet Contains:
Oxycodone Hydrochloride, USP ..... 80 mg

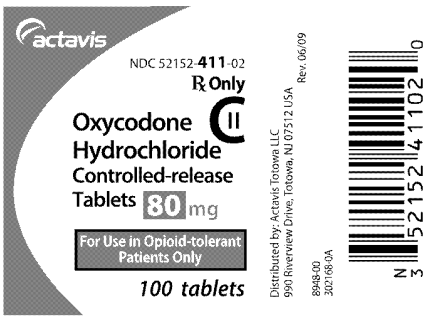
Usual Dosage: See package outsert for full prescribing information.

Swallow tablets whole. Do not crush, break, or chew.

Dispense in a tight, light-resistant container.

Store at 20°-25°C (68°-77°F); with excursions permitted between 15°-30°C (59°-86°F) [See USP Controlled Room Temperature].

U.S. Patent Nos.: 5,508,042; 7,129,248



Distributed by: Actavis Totowa LLC
990 Riverview Drive, Totowa, NJ 07512 USA

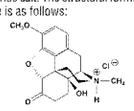
Rev. 06/09

8948-00
302168-0A

N 3 52152 41102 0

WARNING:
Oxycodone hydrochloride extended-release is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.
Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.
Oxycodone hydrochloride extended-release tablets are NOT intended for use as a prn analgesic.
Oxycodone hydrochloride extended-release 60 mg, 80 mg and 160 mg tablets, or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg or total daily doses greater than 80 mg may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effect of opiods.
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION
Oxycodone hydrochloride extended-release tablets are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83

The chemical formula is 4,5α-epoxy-14-hydroxy-3-methyoxy-17-methylmorphinan-6-one hydrochloride. Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water artition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hypromellose, lactose, magnesium stearate, polyethylene glycol 400, povidone, sodium hydroxide, sorbic acid, stearyl alcohol, talc, titanium dioxide, and triacetin.
The 10 mg tablets also contain: hydroxypropyl cellulose.
The 20 mg tablets also contain: polysorbate 80 and red iron oxide.
The 40 mg tablets also contain: polysorbate 80 and yellow iron oxide.
The 80 mg tablets also contain: FD&C blue No. 2, hydroxypropyl cellulose, and yellow iron oxide.

CLINICAL PHARMACOLOGY
Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose, the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.
Central Nervous System
The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.
Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.
Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.
Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of oxycodone hydrochloride extended-release overdose (See **OVERDOSAGE**)
Gastrointestinal Tract And Other Smooth Muscle
Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.
Cardiovascular System
Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.
Concentration – Efficacy Relationships
Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall "drug effect", analgesia and feelings of "relaxation".
As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.
Concentration – Adverse Experience Relationships
Oxycodone hydrochloride extended-release tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.
As with all opioids, the dose must be individualized (see **DOSAGE AND ADMINISTRATION**), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.
PHARMACOKINETICS AND METABOLISM
The activity of oxycodone hydrochloride extended-release tablets is primarily due to the parent drug oxycodone. Oxycodone hydrochloride extended-release tablets are designed to provide controlled delivery of oxycodone over 12 hours.
Breaking, chewing or crushing oxycodone hydrochloride extended-release tablets eliminates the controlled delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.
Oxycodone release from oxycodone hydrochloride extended-release tablets is pH independent. Oxycodone is well absorbed from oxycodone hydrochloride extended-release tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of oxycodone hydrochloride extended-release to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Dose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of oxycodone hydrochloride extended-release was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.
Absorption
About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers, the t½ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, oxycodone hydrochloride extended-release tablets exhibit a biphasic absorption pattern with two apparent absorption half-lives of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.
Plasma Oxycodone by Time
Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Another study established that the 160 mg tablet is bioequivalent to 2 x 80 mg tablets as well as to 4 x 40 mg for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 2 below). Given the short half-life of elimination of oxycodone from oxycodone hydrochloride extended-release, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with oxycodone hydrochloride extended-release tablets. In a study comparing 10 mg of oxycodone hydrochloride extended-release every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations.

Plasma Oxycodone By Time

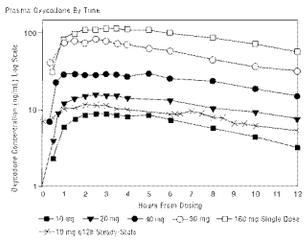


TABLE 1
Mean [% coefficient variation]

Regimen/ Dosage Form	AUC (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose 10 mg Oxycodone Hydrochloride Extended-release	100.7 [26.6]	10.6 [29.1]	2.7 [44.1]	n.a.
20 mg Oxycodone Hydrochloride Extended-release	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
40 mg Oxycodone Hydrochloride Extended-release	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
80 mg Oxycodone Hydrochloride Extended-release*	1085.5 [32.3]	96.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose 10 mg Oxycodone Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [30.9]

TABLE 2
Mean [% coefficient variation]

Regimen/ Dosage Form	AUC† (ng•hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose 4 x 40 mg Oxycodone Hydrochloride Extended-release*	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
2 x 80 mg Oxycodone Hydrochloride Extended-release*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
1 x 160 mg Oxycodone Hydrochloride Extended-release*	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

† for single-dose AUC = AUC_{0-inf}; for multiple-dose AUC = AUC_{0-T}
* data obtained while volunteers received naltrexone which can enhance absorption

Oxycodone hydrochloride Extended-Release is NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that oxycodone hydrochloride extended-release tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.
Food Effects
Food has no significant effect on the extent of absorption of oxycodone from oxycodone hydrochloride extended-release. However, the peak plasma concentration of oxycodone increased by 25% when a oxycodone hydrochloride extended-release 160 mg tablet was administered with a high-fat meal.
Distribution
Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see **PRECAUTIONS**).
Metabolism
Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.
The formation of oxymorphone, but not noroxycodone, is mediated by cytochrome P450 2D6 and, cytochrome P450 3A4, respectively. In addition, noroxymorphone formation is mediated by both cytochrome P450 2D6 and cytochrome P450 3A4. Therefore, the formation of these metabolites can in theory be affected by other drugs (see **Drug-Drug Interactions**).
Excretion
Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤ 14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.
Special Populations
Elderly
The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.
Gender
Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.
Renal Impairment
Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in t½ of elimination for oxycodone of only 1 hour (see **PRECAUTIONS**).
Hepatic Impairment
Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%.
These differences are accompanied by increases in some, but not other, drug effects. The t½ elimination for oxycodone increased by 2.3 hours (see **PRECAUTIONS**).
Drug-Drug Interactions (see **PRECAUTIONS**)
Oxycodone is metabolized in part by cytochrome P450 2D6 and cytochrome P450 3A4 and in theory can be affected by other drugs.
Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic anti-depressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.
Pharmacodynamics
A single-dose, double-blind, placebo- and dose-controlled study was conducted using oxycodone hydrochloride extended-release (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. Twenty and 30 mg of oxycodone hydrochloride extended-release were superior in reducing pain compared with placebo, and this difference was statistically significant. The onset of analgesic action with oxycodone hydrochloride extended-release occurred within 1 hour in most patients following oral administration.
CLINICAL TRIALS
A double-blind placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with chronic, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, 20 mg oxycodone hydrochloride extended-release q12h but not 10 mg oxycodone hydrochloride extended-release q12h decreased pain compared with placebo, and this difference was statistically significant.
INDICATIONS AND USAGE
Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.
Oxycodone hydrochloride extended-release is NOT intended for use as a prn analgesic.
Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.
Oxycodone hydrochloride extended-release is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. Oxycodone hydrochloride extended-release is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)
CONTRAINDICATIONS
Oxycodone hydrochloride extended-release is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone hydrochloride extended-release is contraindicated in any patient who has or is suspected of having paralytic ileus.
WARNINGS
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.
Oxycodone hydrochloride extended-release 60 mg, 80 mg and 160 mg tablets or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.
Misuse, Abuse and Diversion of Opioids
Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.
Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing oxycodone hydrochloride extended-release in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
Oxycodone hydrochloride extended-release has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).
Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.
Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.
Interactions with Alcohol and Drugs of Abuse
Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.
DRUG ABUSE AND ADDICTION
Oxycodone hydrochloride extended-release is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.
Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. There is a potential for drug addiction to develop following exposure to opioids, including oxycodone.
Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.
"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.
Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Oxycodone hydrochloride extended-release, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.
Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.
Oxycodone hydrochloride extended-release consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.
Respiratory Depression
Respiratory depression is the chief hazard from oxycodone, the active ingredient in oxycodone hydrochloride extended-release, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.
Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.
Head Injury
The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.
Hypotensive Effect
Oxycodone hydrochloride extended-release may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.
PRECAUTIONS
General
Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.
Use of oxycodone hydrochloride extended-release is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.
The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.
Interactions with other CNS Depressants
Oxycodone hydrochloride extended-release should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of oxycodone hydrochloride extended-release.
Interactions with Mixed Agonist/Antagonist Opioid Analgesics
Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.
Ambulatory Surgery and Postoperative Use
Oxycodone hydrochloride extended-release is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).
Oxycodone hydrochloride extended-release is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.
Oxycodone hydrochloride extended-release is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.
Oxycodone hydrochloride extended-release is only indi-

PATIENT INFORMATION
OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS
10 mg, 20 mg, 40 mg, 80 mg*
***80 mg for use in opiod-tolerant patients only.** C II

℞ **Only**

Read this information carefully before you take oxycodone hydrochloride extended-release tablets.
Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if oxycodone hydrochloride extended-release is right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information I Should Know About Oxycodone Hydrochloride Extended-Release?
- **Use oxycodone hydrochloride extended-release the way your doctor tells you to.**
- **Use oxycodone hydrochloride extended-release only for the condition for which it was prescribed.**
- **Oxycodone hydrochloride extended-release is not for occasional ("as needed") use.**
- **Swallow the tablets whole.** Do not break, crush, dissolve, or chew them before swallowing. Oxycodone hydrochloride extended-release works properly over 12 hours only when swallowed whole. **If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.**
- **Keep oxycodone hydrochloride extended-release out of the reach of children.** Accidental overdose by a child is dangerous and may result in death.
- **Prevent theft and misuse.** Oxycodone hydrochloride extended-release contains a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What is Oxycodone Hydrochloride Extended-Release?
Oxycodone hydrochloride extended-release is a tablet that comes in several strengths and contains the medicine oxycodone (ox-e-KOE-done). This medicine is a painkiller like morphine. Oxycodone hydrochloride extended-release treats moderate to severe pain that is expected to last for an extended period of time. Use oxycodone hydrochloride extended-release regularly during treatment. It contains enough medicine to last for up to twelve hours.

Who Should Not Take Oxycodone Hydrochloride Extended-Release?
Do not take oxycodone hydrochloride extended-release if
- your doctor did not prescribe oxycodone hydrochloride extended-release for you.
- your pain is mild or will go away in a few days.
- your pain can be controlled by occasional use of other painkillers.
- you have severe asthma or severe lung problems.
- you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox, Tylenol with Codeine, or Vicodin). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
- you had surgery less than 12 - 24 hours ago and you were not taking oxycodone hydrochloride extended-release just before surgery.

Your doctor should know about all your medical conditions before deciding if oxycodone hydrochloride extended-release is right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:
- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking oxycodone hydrochloride extended-release.

If you are pregnant or plan to become pregnant, talk with your doctor. Oxycodone hydrochloride extended-release may not be right for you.
Tell your doctor if you are breast feeding. Oxycodone hydrochloride

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS 10 mg, 20 mg, 40 mg, 80 mg* C II

8949-00

℞ **Only**

extended-release will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with oxycodone hydrochloride extended-release, especially if they cause drowsiness.

How Should I Take Oxycodone Hydrochloride Extended-Release?

- **Follow your doctor's directions exactly.** Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take oxycodone hydrochloride extended-release more often than prescribed.
- **Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.**
- **If you miss a dose,** take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.
- **In case of overdose,** call your local emergency number or Poison Control Center right away.
- **Review your pain regularly with your doctor** to determine if you still need oxycodone hydrochloride extended-release.
- **You may see tablets in your stools (bowel movements).** Do not be concerned. Your body has already absorbed the medicine.

If you continue to have pain or bothersome side effects, call your doctor.

Stopping oxycodone hydrochloride extended-release. Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking oxycodone hydrochloride extended-release all at once if you have been taking it for more than a few days.

After you stop taking oxycodone hydrochloride extended-release, flush the unused tablets down the toilet.

What Should I Avoid While Taking Oxycodone Hydrochloride Extended-Release?

- **Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities** until you know how you react to this medicine. Oxycodone hydrochloride extended-release can make you sleepy.
- **Do not drink alcohol while using oxycodone hydrochloride extended-release. It may increase the chance of getting dangerous side effects.**
- **Do not take other medicines without your doctor's approval.** Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you sleepy.

What are the Possible Side Effects of Oxycodone Hydrochloride Extended-Release?

Call your doctor or get medical help right away if

- your breathing slows down
- you feel faint, dizzy, confused, or have any other unusual symptoms

Some of the common side effects of oxycodone hydrochloride extended-release are nausea, vomiting, dizziness, drowsiness, constipation, itching, dry mouth, sweating, weakness, and headache. Some of these side effects may decrease with continued use.

There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while using oxycodone hydrochloride extended-release.

These are not all the possible side effects of oxycodone hydrochloride extended-release. For a complete list, ask your doctor or pharmacist.

General Advice About Oxycodone Hydrochloride Extended-Release

- Do not use oxycodone hydrochloride extended-release for conditions for which it was not prescribed.
- Do not give oxycodone hydrochloride extended-release to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems, including death.

This leaflet summarizes the most important information about oxycodone hydrochloride extended-release. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about oxycodone hydrochloride extended-release that is written for health professionals.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

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cated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).

Patients who are already receiving oxycodone hydrochloride extended-release tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

Oxycodone hydrochloride extended-release and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers

If clinically advisable, patients receiving oxycodone hydrochloride extended-release tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that oxycodone hydrochloride extended-release tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that oxycodone hydrochloride extended-release tablets were designed to work properly only if swallowed whole. Oxycodone hydrochloride extended-release tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of oxycodone hydrochloride extended-release without consulting the prescribing professional.
5. Patients should be advised that oxycodone hydrochloride extended-release may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine oxycodone hydrochloride extended-release with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that oxycodone hydrochloride extended-release is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
10. Patients should be advised that if they have been receiving treatment with oxycodone hydrochloride extended-release for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the oxycodone hydrochloride extended-release dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
11. Patients should be instructed to keep oxycodone hydrochloride extended-release in a secure place out of the reach of children. When oxycodone hydrochloride extended-release is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction

Oxycodone hydrochloride extended-release is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including oxycodone hydrochloride extended-release, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part by cytochrome P450 2D6 and cytochrome P450 3A4 and in theory can be affected by other drugs.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

Oxycodone hydrochloride extended-release, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 mcg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 mcg/mL and with activation 48 hours after exposure at doses of up to 5000 mcg/mL, and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 mcg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 mcg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 mcg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

Pregnancy

Teratogenic Effects - Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Oxycodone hydrochloride extended-release is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving oxycodone hydrochloride extended-release because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of oxycodone hydrochloride extended-release have not been established in pediatric patients below the age of 18. **It must be remembered that oxycodone hydrochloride extended-release tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see **PHARMACOKINETICS AND METABOLISM**). Of the total number of subjects (445) in clinical studies of oxycodone hydrochloride extended-release, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received oxycodone hydrochloride extended-release. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of oxycodone hydrochloride extended-release in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

The safety of oxycodone hydrochloride extended-release was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received oxycodone hydrochloride extended-release in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with oxycodone hydrochloride extended-release tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with oxycodone hydrochloride extended-release are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia. In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as oxycodone hydrochloride extended-release therapy is continued and some degree of tolerance is developed.

Clinical trials comparing oxycodone hydrochloride extended-release with immediate-release oxycodone and placebo revealed a similar adverse event profile between oxycodone hydrochloride extended-release and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

TABLE 3

	Oxycodone Hydrochloride Extended-Release (n=227) (%)	Immediate-Release (n=225) (%)	Placebo (n=45) (%)
Constipation	(23)	(26)	(7)
Nausea	(23)	(27)	(11)
Somnolence	(23)	(24)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Vomiting	(12)	(14)	(7)
Headache	(7)	(8)	(7)
Dry Mouth	(6)	(7)	(2)
Asthenia	(6)	(7)	-
Sweating	(5)	(6)	(2)

The following adverse experiences were reported in oxycodone hydrochloride extended-release-treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in post-marketing experience.

Blood and lymphatic system disorders: lymphadenopathy

Cardiac disorders: palpitations (in the context of withdrawal)

Ear and labyrinth disorders: tinnitus

Endocrine disorders: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Eye disorders: abnormal vision

Gastrointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, ileus, increased appetite, stomatitis

General disorders and administration site conditions: chest pain, edema, facial edema, malaise, pain, peripheral edema, thirst, withdrawal syndrome (with and without seizures)

Immune system disorders: anaphylactic or anaphylactoid reaction (symptoms of)

Infections and infestations: pharyngitis

Injury, poisoning and procedural complications: accidental injury

Investigations: hyponatremia, increased hepatic enzymes, ST depression

Metabolism and nutrition disorders: dehydration

Musculoskeletal and connective tissue disorders: neck pain

Nervous system disorders: abnormal gait, amnesia, hyperkinesia, hypertonia (muscular), hypesthesia, hypotonia, migraine, paresthesia, seizures, speech disorder, stupor, syncope, taste perversion, tremor, vertigo

Psychiatric disorders: agitation, depersonalization, depression, emotional lability, hallucination

Renal and urinary disorders: dysuria, hematuria, polyuria, urinary retention, urination impaired

Reproductive system and breast disorders: amenorrhea, decreased libido, impotence

Respiratory, thoracic and mediastinal disorders: cough increased, voice alteration

Skin and subcutaneous tissue disorders: dry skin, exfoliative dermatitis, urticaria

Vascular disorders: vasodilation

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death. Deaths due to overdose have been reported with abuse and misuse of oxycodone hydrochloride extended-release, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when oxycodone hydrochloride extended-release is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including oxycodone hydrochloride extended-release, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE IS AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE. OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCODONE HYDROCHLORIDE EXTENDED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

One oxycodone hydrochloride extended-release 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets (see DOSAGE AND ADMINISTRATION).

Patients should be started on the lowest appropriate dose (see DOSAGE AND ADMINSTRATION: Initiation of Therapy). In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

Oxycodone hydrochloride extended-release tablets are an extended-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. The extended-release nature of the formulation allows oxycodone hydrochloride extended-release to be effectively administered every 12 hours (see **CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM**). While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (see **BOXED WARNING**).

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

(1) the general condition and medical status of the patient;
(2) the daily dose, potency, and kind of the analgesic(s) the patient has been taking;
(3) the reliability of the conversion estimate used to calculate the dose of oxycodone;
(4) the patient's opioid exposure and opioid tolerance (if any);
(5) the **Special Instructions for oxycodone hydrochloride extended-release 60 mg, 80 mg and 160 mg Tablets or a single dose greater than 40 mg**; and
(6) the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of oxycodone hydrochloride extended-release in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see **PRECAUTIONS: Drug-Drug Interactions**).

Experience indicates a reasonable starting dose of oxycodone hydrochloride extended-release for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg q12h. If a non-opioid analgesic is being provided, it may be continued. Oxycodone hydrochloride extended-release should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

For initiation of oxycodone hydrochloride extended-release therapy for patients previously taking opioids, the conversion ratios from Foley, KM. [NEJM, 1985; 313:84-95], found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.
2. When converting from oxycodone, divide the 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of oxycodone hydrochloride extended-release.
3. Round down to a dose which is appropriate for the tablet strengths available.
4. Discontinue all other around-the-clock opioid drugs when oxycodone hydrochloride extended-release therapy is initiated.
5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

TABLE 4

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*

(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	--
Codeine	0.15	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

* **To be used only for conversion to oral oxycodone.** For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia should be made available in the form of a suitable short-acting analgesic.

Oxycodone hydrochloride extended-release can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see **PRECAUTIONS**).

Conversion from Transdermal Fentanyl to Oxycodone Hydrochloride Extended-Release

Eighteen hours following the removal of the transdermal fentanyl patch, oxycodone hydrochloride extended-release treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of oxycodone hydrochloride extended-release, should be initially substituted for each 25 mcg/hr fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naive, will experience side effects. Frequently the side effects from oxycodone hydrochloride extended-release are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with antiemetics or other modalities may relieve these symptoms and should be considered.

Patients receiving oxycodone hydrochloride extended-release may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase. If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family.

Special Instructions for Oxycodone Hydrochloride Extended-Release Tablets 60 mg, 80 mg, and 160 mg or a single dose greater than 40 mg (for use in opioid-tolerant patients only)

Oxycodone hydrochloride extended-release 60 mg, 80 mg, and 160 mg tablets, or a single dose greater than 40 mg, are for use in opioid-tolerant patients only. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

One oxycodone hydrochloride extended-release 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets.

Supplemental Analgesia

Most patients given around-the-clock therapy with controlled-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with oxycodone hydrochloride extended-release tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from Oxycodone Hydrochloride Extended-Release to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING

Oxycodone hydrochloride extended-release tablets are solid dosage forms that contain oxycodone which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

Oxycodone hydrochloride extended-release has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

Oxycodone Hydrochloride Extended-Release Tablets are available as follows:

Oxycodone hydrochloride extended-release tablets 10 mg are round, unscored, white-colored, convex tablets imprinted with OC on one side and 10 on the other. They are supplied as follows: Child resistant closure, opaque plastic bottles of 100 (NDC 52152-408-02).

Oxycodone hydrochloride extended-release tablets 20 mg are round, unscored, pink-colored, convex tablets imprinted with OC on one side and 20 on the other. They are supplied as follows: Child resistant closure, opaque plastic bottles of 100 (NDC 52152-409-02).

Oxycodone hydrochloride extended-release tablets 40 mg are round, unscored, yellow-colored, convex tablets imprinted with OC on one side and 40 on the other. They are supplied as follows: Child resistant closure, opaque plastic bottles of 100 (NDC 52152-410-02).

Oxycodone hydrochloride extended-release tablets 80 mg are round, unscored, green-colored, convex tablets imprinted with OC on one side and 80 on the other. They are supplied as follows: Child resistant closure, opaque plastic bottles of 100 (NDC 52152-411-02).

Store at 20°-25°C (68°-77°F); with excursions permitted between 15°-30°C (59°-86°F)[See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container.

CAUTION

DEA Order Form Required.

actavis

Distributed by: Actavis Totowa LLC
990 Riverview Drive
Totowa, NJ 07512 USA

8949-00 5/09

HDMA Standard Product Information — Pharmaceutical Products

☒ New Item ☐ Promotion/Deal ☐ Open Stock ☐ Post Launch Change

Date: Nov 24, 2009

PRODUCT INFORMATION

Manufacturer/Broker Name: Actavis Totowa LLC Number: 52152

Product Name: Oxycodone controlled release tablets 10mg

Product ID Number:

☒ NDC 52152-408-02 ☒ UPC/GTIN # 3 52152-408-02 0

Description: Round, unscored, white-colored, convex tablets imprinted with OC on one side and 10 on the other

Address: 990 Riverview Drive

City, State, Zip: Totowa, NJ 07512

Key Contact: Jinping McCormick Fax:

Phone Number: 888-925-2342 Ext:

Phone Number: Ext:

Is the Product? ☒ Direct Ship Item ☐ Drop Ship Item

Is the Product a Controlled Drug? ☒ Yes ☐ No

If Yes, Schedule Number: C II

Is this ARCOS reportable? ☐ Yes ☐ No

Is this Product a Legend Device? ☐ Yes ☒ No

Country of Origin: USA

Harmonization Code Number for International Shipping:

Is this product a Hazardous Material or Cytotoxic Agent?

☐ Yes ☒ No If yes, provide additional information on page 2.

Attach copy of Material Safety Data Sheet (MSDS)

Attach Package Insert

SPECIAL HANDLING AND STORAGE REQUIREMENTS

a. Temperature – Indicate the normal temperature range for this product.

I.	Controlled Room Temperature (68° – 77° F)	☒
II.	Room Temperature (59° – 86° F)	☐
III.	Excessive Heat (>104° F)	☐
IV.	Cool (46° – 59° F)	☐
V.	Refrigerated (36° – 46° F)	☐
VI.	Frozen (-4° – 14° F)	☐
VII.	No Requirement	☐

b. Are temperature excursions permitted/allowed for product? ☒ Yes ☐ No

If Yes, provide the temperature range and hours duration:

59 -86F and

c. Are there additional storage and shipping requirements? ☐ Yes ☒ No

If yes, please provide on page 2.

ADDITIONAL PRODUCT INFORMATION

Is there a minimum order quantity?

If yes, ☐ Case ☐ Carton ☒ Item

Number of Pieces? 48

Shelf Life: 35 Months

Whsl. Code #:

Fineline Code:

Is Item? ☐ Unit Dose ☐ Unit of Use

If Unit Dose, is item bar coded to unit dose for Hospital tracking purposes?

☐ Yes ☐ No

Will handling data change in the first:

6 months? ☐ Yes

9 months? ☐ Yes

12 months? ☐ Yes

Unknown? ☐ Yes

ITEM AND PACKING INFORMATION

Size/Strength /Form	Unit Of Sale	UPC Code	Mstr. Shpr.	Inner Case Pk	Wght. Lbs.	Cube	Case Dimensions	Item Dimensions	Pallet Dimensions	# Cases/ Pallet
100/10mg/ CR Tablets	☒ Bottle ☐ Box ☐ Glass jar ☐ Ampule ☐ Other	Case:	48		Case: 4.25 lb	0.37 cu ft	Depth: 11.81"	Depth: 1.83"	Depth: 40"	100
		Carton:			Carton:		Height: 7.38"	Height: 3.28"	Height:	
		Item: 3 5215240802 0			Item: 1.34 oz		Width: 7.31"	Width: 1.63"	Width: 48"	

For Generic Drug Products:

I. Orange Book Rating: AB

II. Product Color: White

III. Brand Name Equivalent: OxyContinr

IV. Generic Name For Brand: Oxycodone CR Tablet

COST INFORMATION

	Regular Cost ($)	Purchase Allowance ☐ OI ☐ BB $	Purchase Allowance ☐ OI ☐ BB %	Distribution Allowance ☐ OI ☐ BB $	Distribution Allowance ☐ OI ☐ BB %	Invoice Cost ($)	Net Cost ($)	Mfr's AWP	Avg Retl Price ($)	SRP ($)	Excise Tax
DZ											
EA						$152.67		$183.28			
PPK											

This offer is made on a proportionally equal basis to all sellers' accounts completive with customer. **Signature:**

Revised 02/21/06

Item Description: Oxycodone CR Tablets **Manufacturer:** Actavis Totowa LLC

If additional information is necessary, provide on right of page or as attachment.

HAZARDOUS MATERIAL INFORMATION

Is this product:

- a) Cytotoxic? ☐ Yes ☒ No
- b) Carcinogen? ☐ Yes ☒ No
- c) Inhalation Hazard? ☐ Yes ☒ No
- d) Contact Hazard? ☐ Yes ☒ No

Is this item considered a carcinogen? ☐ Yes ☒ No

Is this item an aerosol requiring special storage? ☐ Yes ☒ No

Does this product require special clean-up instructions? ☐ Yes ☒ No

If yes, attach MSDS with special instructions.

Department of Transportation (DOT) I.D. Number: _____

Hazard Class/ORM Code: _____

OSHA/DOT CHEMICAL STORAGE CLASS

Please check appropriate Class(s) for this product.

☒ ORGANIC	☐ ANTINEOPLASTIC
☐ INORGANIC	☐ STEROID/ANDROGEN
☐ CORROSIVE/OXIDIZER	☐ ESSENTIAL CHEMICAL
☐ AEROSOL	☐ PRECURSOR CHEMICAL (Describe below)
☐ AEROSOL CLASS	☐ MAXIMUM QTY LEVEL

Is the product restricted for air shipping?

- ☐ Passenger
- ☐ Cargo
- ☐ Passenger & Cargo

Precursor Chemical:			Size/Strength
Ephedrine	☐ Yes	☒ No	_____
Pseudoephedrine	☐ Yes	☒ No	_____
Phenylpropanolamine	☐ Yes	☒ No	_____

ADDITIONAL STORAGE AND SHIPPING REQUIREMENTS

Is this product to be shipped to customers on ice? ☐ Yes ☒ No

Is this product to be shipped to customers on dry ice? ☐ Yes ☒ No

Does this product require refrigerated truck for transport? ☐ Yes ☒ No

Is this Product State Regulated? ☐ Yes ☐ No

If yes, list states on the right or as an attachment.

Are there special returns requirements? ☐ Yes ☒ No

If yes, provide requirements in the space to the right or as attachment.

ADDITIONAL INFORMATION AS NECESSARY

HDMA Standard Product Information — Pharmaceutical Products

☒ New Item ☐ Promotion/Deal ☐ Open Stock ☐ Post Launch Change

Date: Nov 24, 2009

PRODUCT INFORMATION

Manufacturer/Broker Name: Actavis Totowa LLC Number: 52152

Product Name: Oxycodone controlled release tablets 20mg

Product ID Number:

☒ NDC 52152-409-02 ☒ UPC/GTIN # 3 52152-409-02 7

Description: Round, unscored, pink-colored, convex tablets imprinted with OC on one side and 20 on the other

Address: 990 Riverview Drive

City, State, Zip: Totowa, NJ 07512

Key Contact: Jinping McCormick Fax:

Phone Number: 888-925-2342 Ext:

Phone Number: Ext:

Is the Product? ☒ Direct Ship Item ☐ Drop Ship Item

Is the Product a Controlled Drug? ☒ Yes ☐ No

If Yes, Schedule Number: C II

Is this ARCOS reportable? ☐ Yes ☐ No

Is this Product a Legend Device? ☐ Yes ☒ No

Country of Origin: USA

Harmonization Code Number for International Shipping:

Is this product a Hazardous Material or Cytotoxic Agent?

☐ Yes ☒ No If yes, provide additional information on page 2.

Attach copy of Material Safety Data Sheet (MSDS)

Attach Package Insert

SPECIAL HANDLING AND STORAGE REQUIREMENTS

a. Temperature – Indicate the normal temperature range for this product.

I.	Controlled Room Temperature (68° – 77° F)	☒
II.	Room Temperature (59° – 86° F)	☐
III.	Excessive Heat (>104° F)	☐
IV.	Cool (46° – 59° F)	☐
V.	Refrigerated (36° – 46° F)	☐
VI.	Frozen (-4° – 14° F)	☐
VII.	No Requirement	☐

b. Are temperature excursions permitted/allowed for product? ☒ Yes ☐ No

If Yes, provide the temperature range and hours duration:

59 -86F and

c. Are there additional storage and shipping requirements? ☐ Yes ☒ No

If yes, please provide on page 2.

ADDITIONAL PRODUCT INFORMATION

Is there a minimum order quantity?

If yes, ☐ Case ☐ Carton ☒ Item

Number of Pieces? 48

Shelf Life: 35 Months

Whsl. Code #:

Fineline Code:

Is Item? ☐ Unit Dose ☐ Unit of Use

If Unit Dose, is item bar coded to unit dose for Hospital tracking purposes?

☐ Yes ☐ No

Will handling data change in the first:

6 months? ☐ Yes

9 months? ☐ Yes

12 months? ☐ Yes

Unknown? ☐ Yes

ITEM AND PACKING INFORMATION

Size/Strength /Form	Unit Of Sale	UPC Code	Mstr. Shpr.	Inner Case Pk	Wght. Lbs.	Cube	Case Dimensions	Item Dimensions	Pallet Dimensions	# Cases/ Pallet
100/20mg/ CR Tablets	☒ Bottle ☐ Box ☐ Glass jar ☐ Ampule ☐ Other	Case:	48		Case: 4.25 lb	0.37 cu ft	Depth: 11.81"	Depth: 1.83"	Depth: 40"	100
		Carton:			Carton:		Height: 7.38"	Height: 3.28"	Height:	
		Item: 3 5215240902 7			Item: 1.34 oz		Width: 7.31"	Width: 1.63"	Width: 48"	

For Generic Drug Products:

I. Orange Book Rating: AB

II. Product Color: Pink

III. Brand Name Equivalent: OxyContinr

IV. Generic Name For Brand: Oxycodone CR Tablet

COST INFORMATION

	Regular Cost ($)	Purchase Allowance ☐ OI ☐ BB $	Purchase Allowance ☐ OI ☐ BB %	Distribution Allowance ☐ OI ☐ BB $	Distribution Allowance ☐ OI ☐ BB %	Invoice Cost ($)	Net Cost ($)	Mfr's AWP	Avg Retl Price ($)	SRP ($)	Excise Tax
DZ											
EA						$292.12		$350.69			
PPK											

This offer is made on a proportionally equal basis to all sellers' accounts completive with customer. **Signature:**

Revised 02/21/06

Item Description: Oxycodone CR Tablets **Manufacturer:** Actavis Totowa LLC

If additional information is necessary, provide on right of page or as attachment.

HAZARDOUS MATERIAL INFORMATION

Is this product:

- a) Cytotoxic? ☐ Yes ☒ No
- b) Carcinogen? ☐ Yes ☒ No
- c) Inhalation Hazard? ☐ Yes ☒ No
- d) Contact Hazard? ☐ Yes ☒ No

Is this item considered a carcinogen? ☐ Yes ☒ No

Is this item an aerosol requiring special storage? ☐ Yes ☒ No

Does this product require special clean-up instructions? ☐ Yes ☒ No

If yes, attach MSDS with special instructions.

Department of Transportation (DOT) I.D. Number: _____

Hazard Class/ORM Code: _____

OSHA/DOT CHEMICAL STORAGE CLASS

Please check appropriate Class(s) for this product.

☒ ORGANIC	☐ ANTINEOPLASTIC
☐ INORGANIC	☐ STEROID/ANDROGEN
☐ CORROSIVE/OXIDIZER	☐ ESSENTIAL CHEMICAL
☐ AEROSOL	☐ PRECURSOR CHEMICAL (Describe below)
☐ AEROSOL CLASS	☐ MAXIMUM QTY LEVEL

Is the product restricted for air shipping?

- ☐ Passenger
- ☐ Cargo
- ☐ Passenger & Cargo

Precursor Chemical:			Size/Strength
Ephedrine	☐ Yes	☒ No	_____
Pseudoephedrine	☐ Yes	☒ No	_____
Phenylpropanolamine	☐ Yes	☒ No	_____

ADDITIONAL STORAGE AND SHIPPING REQUIREMENTS

Is this product to be shipped to customers on ice? ☐ Yes ☒ No

Is this product to be shipped to customers on dry ice? ☐ Yes ☒ No

Does this product require refrigerated truck for transport? ☐ Yes ☒ No

Is this Product State Regulated? ☐ Yes ☐ No

If yes, list states on the right or as an attachment.

Are there special returns requirements? ☐ Yes ☒ No

If yes, provide requirements in the space to the right or as attachment.

ADDITIONAL INFORMATION AS NECESSARY

HDMA Standard Product Information — Pharmaceutical Products

☒ New Item ☐ Promotion/Deal ☐ Open Stock ☐ Post Launch Change

Date: Nov 24, 2009

PRODUCT INFORMATION

Manufacturer/Broker Name: Actavis Totowa LLC Number: 52152

Product Name: Oxycodone controlled release tablets 40mg

Product ID Number:

☒ NDC 52152-410-02 ☒ UPC/GTIN # 3 52152-410-02 3

Description: Round, unscored, yellow-colored, convex tablets imprinted with OC on one side and 40 on the other

Address: 990 Riverview Drive

City, State, Zip: Totowa, NJ 07512

Key Contact: Jinping McCormick Fax:

Phone Number: 888-925-2342 Ext:

Phone Number: Ext:

Is the Product? ☒ Direct Ship Item ☐ Drop Ship Item

Is the Product a Controlled Drug? ☒ Yes ☐ No

If Yes, Schedule Number: C II

Is this ARCOS reportable? ☐ Yes ☐ No

Is this Product a Legend Device? ☐ Yes ☒ No

Country of Origin: USA

Harmonization Code Number for International Shipping:

Is this product a Hazardous Material or Cytotoxic Agent?

☐ Yes ☒ No If yes, provide additional information on page 2.

Attach copy of Material Safety Data Sheet (MSDS)

Attach Package Insert

SPECIAL HANDLING AND STORAGE REQUIREMENTS

a. Temperature – Indicate the normal temperature range for this product.

I.	Controlled Room Temperature (68° – 77° F)	☒
II.	Room Temperature (59° – 86° F)	☐
III.	Excessive Heat (>104° F)	☐
IV.	Cool (46° – 59° F)	☐
V.	Refrigerated (36° – 46° F)	☐
VI.	Frozen (-4° – 14° F)	☐
VII.	No Requirement	☐

b. Are temperature excursions permitted/allowed for product? ☒ Yes ☐ No

If Yes, provide the temperature range and hours duration:

59 -86F and

c. Are there additional storage and shipping requirements? ☐ Yes ☒ No

If yes, please provide on page 2.

ADDITIONAL PRODUCT INFORMATION

Is there a minimum order quantity?

If yes, ☐ Case ☐ Carton ☒ Item

Number of Pieces? 48

Shelf Life: 35 Months

Whsl. Code #:

Fineline Code:

Is Item? ☐ Unit Dose ☐ Unit of Use

If Unit Dose, is item bar coded to unit dose for Hospital tracking purposes?

☐ Yes ☐ No

Will handling data change in the first:

6 months? ☐ Yes

9 months? ☐ Yes

12 months? ☐ Yes

Unknown? ☐ Yes

ITEM AND PACKING INFORMATION

Size/Strength /Form	Unit Of Sale	UPC Code	Mstr. Shpr.	Inner Case Pk	Wght. Lbs.	Cube	Case Dimensions	Item Dimensions	Pallet Dimensions	# Cases/ Pallet
100/40mg/ CR Tablets	☒ Bottle ☐ Box ☐ Glass jar ☐ Ampule ☐ Other	Case:	48		Case: 4.25 lb	0.37 cu ft	Depth: 11.81"	Depth: 1.83"	Depth: 40"	100
		Carton:			Carton:		Height: 7.38"	Height: 3.28"	Height:	
		Item: 3 5215241002 3			Item: 1.34 oz		Width: 7.31"	Width: 1.63"	Width: 48"	

For Generic Drug Products:

I. Orange Book Rating: AB

II. Product Color: yellow

III. Brand Name Equivalent: OxyContinr

IV. Generic Name For Brand: Oxycodone CR Tablet

COST INFORMATION

	Regular Cost ($)	Purchase Allowance ☐ OI ☐ BB $	Purchase Allowance ☐ OI ☐ BB %	Distribution Allowance ☐ OI ☐ BB $	Distribution Allowance ☐ OI ☐ BB %	Invoice Cost ($)	Net Cost ($)	Mfr's AWP	Avg Retl Price ($)	SRP ($)	Excise Tax
DZ											
EA						$518.33		$622.25			
PPK											

This offer is made on a proportionally equal basis to all sellers' accounts completive with customer. **Signature:**

Revised 02/21/06

Item Description: Oxycodone CR Tablets **Manufacturer:** Actavis Totowa LLC

If additional information is necessary, provide on right of page or as attachment.

HAZARDOUS MATERIAL INFORMATION

Is this product:

- a) Cytotoxic? ☐ Yes ☒ No
- b) Carcinogen? ☐ Yes ☒ No
- c) Inhalation Hazard? ☐ Yes ☒ No
- d) Contact Hazard? ☐ Yes ☒ No

Is this item considered a carcinogen? ☐ Yes ☒ No

Is this item an aerosol requiring special storage? ☐ Yes ☒ No

Does this product require special clean-up instructions? ☐ Yes ☒ No

If yes, attach MSDS with special instructions.

Department of Transportation (DOT) I.D. Number: _____

Hazard Class/ORM Code: _____

OSHA/DOT CHEMICAL STORAGE CLASS

Please check appropriate Class(s) for this product.

☒ ORGANIC	☐ ANTINEOPLASTIC
☐ INORGANIC	☐ STEROID/ANDROGEN
☐ CORROSIVE/OXIDIZER	☐ ESSENTIAL CHEMICAL
☐ AEROSOL	☐ PRECURSOR CHEMICAL (Describe below)
☐ AEROSOL CLASS	☐ MAXIMUM QTY LEVEL

Is the product restricted for air shipping?

- ☐ Passenger
- ☐ Cargo
- ☐ Passenger & Cargo

Precursor Chemical:			Size/Strength
Ephedrine	☐ Yes	☒ No	_____
Pseudoephedrine	☐ Yes	☒ No	_____
Phenylpropanolamine	☐ Yes	☒ No	_____

ADDITIONAL STORAGE AND SHIPPING REQUIREMENTS

Is this product to be shipped to customers on ice? ☐ Yes ☒ No

Is this product to be shipped to customers on dry ice? ☐ Yes ☒ No

Does this product require refrigerated truck for transport? ☐ Yes ☒ No

Is this Product State Regulated? ☐ Yes ☐ No

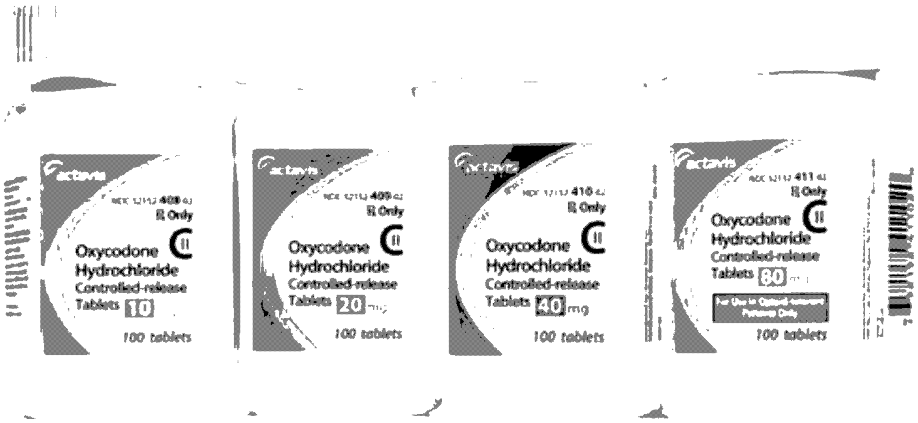
If yes, list states on the right or as an attachment.

Are there special returns requirements? ☐ Yes ☒ No

If yes, provide requirements in the space to the right or as attachment.

ADDITIONAL INFORMATION AS NECESSARY

Now... more choices for pain management.



Oxycodone Hydrochloride Controlled-release Tablets, available from Actavis.

- Compare to OxyContin®*
- Dosage strengths of 10 mg, 20 mg, 40 mg and 80 mg
- 100-count bottles
- Another controlled-release product in our portfolio

To learn more, contact your Actavis representative or wholesaler, or call customer service at 888.925.2342.

Product	Strength	Size	NDC#
Oxycodone HCl CR Tablets	10 mg	100	52152-408-02
Oxycodone HCl CR Tablets	20 mg	100	52152-409-02
Oxycodone HCl CR Tablets	40 mg	100	52152-410-02
Oxycodone HCl CR Tablets	80 mg	100	52152-411-02

Please see adjacent pages for prescribing information.

A260 Rev. 9/2009

*OxyContin® is the registered trademark of Purdue Pharma L.P.

actavis
creating value in pharmaceuticals

OXYCODONE HCl CONTROLLED-RELEASE TABLETS

CII

10 mg, 20 mg, 40 mg, 80 mg*

R_x Only

*80 mg, and 160 mg is for use in opioid-tolerant patients only

WARNING:
Oxycodone HCl Controlled-Release Tablets are an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Oxycodone HCl Controlled-Release Tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Oxycodone HCl Controlled-Release Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

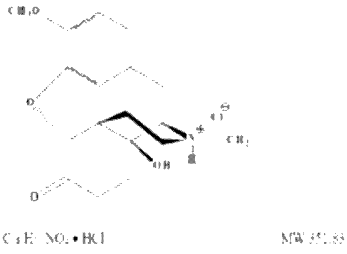
Oxycodone HCl Controlled-Release Tablets are NOT intended for use as a prn analgesic.

OXYCODONE HCl CONTROLLED-RELEASE 80 mg, and 160 mg Tablets, or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

OXYCODONE HCl CONTROLLED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCODONE HCl CONTROLLED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

Oxycodone HCl Controlled-Release Tablets are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for oral administration. The tablet strengths describe the amount of oxycodone per tablet as the hydrochloride salt. The structural formula for oxycodone hydrochloride is as follows:



$C_{18}H_{21}NO_4 \cdot HCl$ MW 351.83

The chemical formula is 4, 5α-epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride.

Oxycodone is a white, odorless crystalline powder derived from the opium alkaloid, thebaine. Oxycodone hydrochloride dissolves in water (1 g in 6 to 7 mL). It is slightly soluble in alcohol (octanol water partition coefficient 0.7). The tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hypromellose, lactose, magnesium stearate, polyethylene glycol 400, povidone, sodium hydroxide, sorbic acid, stearyl alcohol, talc, titanium dioxide, and triacetin.

The 10 mg tablets also contain: hydroxypropyl cellulose.

The 20 mg tablets also contain: polysorbate 80 and red iron oxide.

The 40 mg tablets also contain: polysorbate 80 and yellow iron oxide.

The 80 mg tablets also contain: FD&C blue No. 2, hydroxypropyl cellulose, and yellow iron oxide.

Oxycodone HCl controlled-release 10 mg, 20 mg, 40 mg, and 80 mg tablets are tested using USP Dissolution Test 2 and meet the associated tolerances provided in Acceptance Table 2 of the Oxycodone Hydrochloride Extended-Release Tablets USP Monograph.

CLINICAL PHARMACOLOGY

Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, hydromorphone, fentanyl, codeine, and hydrocodone. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, as well as analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence and respiratory depression.

Central Nervous System

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of Oxycodone HCl Controlled-Release Tablets overdose (See **OVERDOSAGE**).

Gastrointestinal Tract And Other Smooth Muscle

Oxycodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration – Efficacy Relationships

Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects, such as pupillary constriction, sedation, overall "drug effect", analgesia and feelings of "relaxation".

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients must be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration – Adverse Experience Relationships

Oxycodone HCl Controlled-Release Tablets are associated with typical opioid-related adverse experiences. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is not clinically relevant.

As with all opioids, the dose must be individualized (see **DOSAGE AND ADMINISTRATION**), because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

PHARMACOKINETICS AND METABOLISM

The activity of Oxycodone HCl Controlled-Release Tablets is primarily due to the parent drug oxycodone. Oxycodone HCl Controlled-Release Tablets are designed to provide controlled delivery of oxycodone over 12 hours.

Breaking, chewing or crushing Oxycodone HCl Controlled-Release Tablets eliminates the controlled delivery mechanism and results in the rapid release and absorption of a potentially fatal dose of oxycodone.

Oxycodone release from Oxycodone HCl Controlled-Release Tablets is pH independent. Oxycodone is well absorbed from Oxycodone HCl Controlled-Release Tablets with an oral bioavailability of 60% to 87%. The relative oral bioavailability of Oxycodone HCl Controlled-Release Tablets to immediate-release oral dosage forms is 100%. Upon repeated dosing in normal volunteers in pharmacokinetic studies, steady-state levels were achieved within 24-36 hours. Dose proportionality and/or bioavailability has been established for the 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for both peak plasma levels (C_{max}) and extent of absorption (AUC). Oxycodone is extensively metabolized and eliminated primarily in the urine as both conjugated and unconjugated metabolites. The apparent elimination half-life of oxycodone following the administration of Oxycodone HCl Controlled-Release Tablets was 4.5 hours compared to 3.2 hours for immediate-release oxycodone.

Absorption

About 60% to 87% of an oral dose of oxycodone reaches the central compartment in comparison to a parenteral dose. This high oral bioavailability is due to low pre-systemic and/or first-pass metabolism. In normal volunteers, the t½ of absorption is 0.4 hours for immediate-release oral oxycodone. In contrast, Oxycodone HCl Controlled-Release Tablets exhibit a biphasic absorption pattern with two apparent absorption half-lives of 0.6 and 6.9 hours, which describes the initial release of oxycodone from the tablet followed by a prolonged release.

Plasma Oxycodone by Time

Dose proportionality has been established for the 10 mg, 20 mg, 40 mg, and 80 mg tablet strengths for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 1 below). Another study established that the 160 mg tablet is bioequivalent to 2 x 80 mg tablets as well as to 4 x 40 mg for both peak plasma concentrations (C_{max}) and extent of absorption (AUC) (see Table 2 below). Given the short half-life of elimination of oxycodone from Oxycodone HCl Controlled-Release Tablets, steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with Oxycodone HCl Controlled-Release Tablets. In a study comparing 10 mg of Oxycodone HCl Controlled-Release Tablets every 12 hours to 5 mg of immediate-release oxycodone every 6 hours, the two treatments were found to be equivalent for AUC and C_{max}, and similar for C_{min} (trough) concentrations.

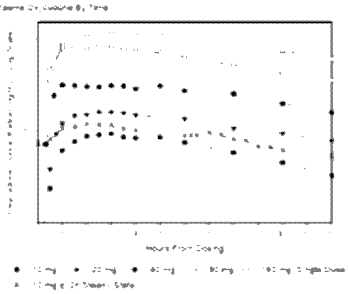


Table 1
Mean [% coefficient variation]

Regimen/	Dosage Form	AUC (ng·hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	10 mg Oxycodone HCl Controlled-Release Tablets	100.7 [26.6]	10.6 [20.1]	2.7 [44.1]	n.a.
	20 mg Oxycodone HCl Controlled-Release Tablets	207.5 [35.9]	21.4 [36.6]	3.2 [57.9]	n.a.
	40 mg Oxycodone HCl Controlled-Release Tablets	423.1 [33.3]	39.3 [34.0]	3.1 [77.4]	n.a.
	80 mg Oxycodone HCl Controlled-Release Tablets*	1085.5 [32.3]	98.5 [32.1]	2.1 [52.3]	n.a.
Multiple Dose	10 mg Oxycodone HCl Controlled-Release Tablets q12h	103.6 [38.6]	15.1 [31.0]	3.2 [69.5]	7.2 [48.1]
	5 mg immediate-release q6h	99.0 [36.2]	15.5 [28.8]	1.6 [49.7]	7.4 [50.9]

Table 2
Mean [% coefficient variation]

Regimen/	Dosage Form	AUC∞ (ng·hr/mL)†	C_{max} (ng/mL)	T_{max} (hrs)	Trough Conc. (ng/mL)
Single Dose	4 x 40 mg Oxycodone HCl Controlled-Release Tablets*	1935.3 [34.7]	152.0 [28.9]	2.56 [42.3]	n.a.
	2 x 80 mg Oxycodone HCl Controlled-Release Tablets*	1859.3 [30.1]	153.4 [25.1]	2.78 [69.3]	n.a.
	1 x 160 mg Oxycodone HCl Controlled-Release Tablets*	1856.4 [30.5]	156.4 [24.8]	2.54 [36.4]	n.a.

† for single-dose AUC = $AUC_{0-\infty}$; for multiple-dose AUC = $AUC_{0-\tau}$
* data obtained while volunteers received naltrexone which can enhance absorption

Oxycodone HCl Controlled-Release Tablets are NOT INDICATED FOR RECTAL ADMINISTRATION. Data from a study involving 21 normal volunteers show that Oxycodone HCl Controlled-Release Tablets administered per rectum resulted in an AUC 39% greater and a C_{max} 9% higher than tablets administered by mouth. Therefore, there is an increased risk of adverse events with rectal administration.

Food Effects

Food has no significant effect on the extent of absorption of oxycodone from Oxycodone HCl Controlled-Release Tablets. However, the peak plasma concentration of oxycodone increased by 25% when an Oxycodone HCl Controlled-Release Tablets 160 mg Tablet was administered with a high-fat meal.

Distribution

Following intravenous administration, the volume of distribution (Vss) for oxycodone was 2.6 L/kg. Oxycodone binding to plasma protein at 37°C and a pH of 7.4 was about 45%. Once absorbed, oxycodone is distributed to skeletal muscle, liver, intestinal tract, lungs, spleen, and brain. Oxycodone has been found in breast milk (see **PRECAUTIONS**).

Metabolism

Oxycodone hydrochloride is extensively metabolized to noroxycodone, oxymorphone, noroxymorphone, and their glucuronides. The major circulating metabolite is noroxycodone with an AUC ratio of 0.6 relative to that of oxycodone. Noroxycodone is reported to be a considerably weaker analgesic than oxycodone. Oxymorphone, although possessing analgesic activity, is present in the plasma only in low concentrations. The correlation between oxymorphone concentrations and opioid effects was much less than that seen with oxycodone plasma concentrations. The analgesic activity profile of other metabolites is not known.

The formation of oxymorphone and noroxycodone, is mediated by cytochrome P450 2D6 and cytochrome P450 3A4, respectively. In addition, noroxymorphone formation is mediated by both cytochrome P450 2D6 and cytochrome P450 3A4. Therefore, the formation of these metabolites can, in theory, be affected by other drugs (see **Drug-Drug Interactions**).

Excretion

Oxycodone and its metabolites are excreted primarily via the kidney. The amounts measured in the urine have been reported as follows: free oxycodone up to 19%; conjugated oxycodone up to 50%; free oxymorphone 0%; conjugated oxymorphone ≤14%; both free and conjugated noroxycodone have been found in the urine but not quantified. The total plasma clearance was 0.8 L/min for adults.

Special Populations

Elderly

The plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly as compared to young subjects.

Gender

Female subjects have, on average, plasma oxycodone concentrations up to 25% higher than males on a body weight adjusted basis. The reason for this difference is unknown.

Renal Impairment

Data from a pharmacokinetic study involving 13 patients with mild to severe renal dysfunction (creatinine clearance <60 mL/min) show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, and AUC values for oxycodone, noroxycodone, and oxymorphone 60%, 50%, and 40% higher than normal subjects, respectively. This is accompanied by an increase in sedation but not by differences in respiratory rate, pupillary constriction, or several other measures of drug effect. There was an increase in t½ of elimination for oxycodone of only 1 hour (see **PRECAUTIONS**).

Hepatic Impairment

Data from a study involving 24 patients with mild to moderate hepatic dysfunction show peak plasma oxycodone and noroxycodone concentrations 50% and 20% higher, respectively, than normal subjects. AUC values are 95% and 65% higher, respectively. Oxymorphone peak plasma concentrations and AUC values are lower by 30% and 40%. These differences are accompanied by increases in some, but not other, drug effects. The t½ elimination for oxycodone increased by 2.3 hours (see **PRECAUTIONS**).

Drug-Drug Interactions (see PRECAUTIONS)

Oxycodone is metabolized in part by cytochrome P450 2D6 and cytochrome P450 3A4 and in theory can be affected by other drugs.

Oxycodone is metabolized in part by cytochrome P450 2D6 to oxymorphone which represents less than 15% of the total administered dose. This route of elimination may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic anti-depressants). However, in a study involving 10 subjects using quinidine, a known inhibitor of cytochrome P450 2D6, the pharmacodynamic effects of oxycodone were unchanged.

Pharmacodynamics

A single-dose, double-blind, placebo- and dose-controlled study was conducted using Oxycodone HCl Controlled-Release Tablets (10, 20, and 30 mg) in an analgesic pain model involving 182 patients with moderate to severe pain. Twenty and 30 mg of Oxycodone HCl Controlled-Release Tablets were superior in reducing pain compared with placebo, and this difference was statistically significant. The onset of analgesic action with Oxycodone HCl Controlled-Release Tablets occurred within 1 hour in most patients following oral administration.

CLINICAL TRIALS

A double-blind placebo-controlled, fixed-dose, parallel group, two-week study was conducted in 133 patients with chronic, moderate to severe pain, who were judged as having inadequate pain control with their current therapy. In this study, 20 mg Oxycodone HCl Controlled-Release Tablets q12h but not 10 mg Oxycodone HCl Controlled-Release Tablets q12h decreased pain compared with placebo, and this difference was statistically significant.

INDICATIONS AND USAGE

Oxycodone HCl Controlled-Release Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

Oxycodone HCl Controlled-Release Tablets are **NOT** intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

Oxycodone HCl Controlled-Release Tablets are not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. Oxycodone HCl Controlled-Release Tablets are only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

Oxycodone HCl Controlled-Release Tablets are contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. Oxycodone HCl Controlled-Release Tablets are contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

OXYCODONE HCl CONTROLLED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCODONE HCl CONTROLLED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

Oxycodone HCl Controlled-Release 80 mg Tablets, or a single dose greater than 40 mg, ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. A single dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids.

Oxycodone HCl Controlled-Release 80 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more. Care should be taken in the prescribing of this tablet strength. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Oxycodone HCl Controlled-Release Tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Oxycodone HCl Controlled-Release Tablets have been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

Oxycodone HCl Controlled-Release Tablets contain oxycodone which is a full mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. There is a potential for drug addiction to develop following exposure to opioids, including oxycodone. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Oxycodone HCl Controlled-Release Tablets, like other opioids, have been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Oxycodone HCl Controlled-Release Tablets consist of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in Oxycodone HCl Controlled-Release Tablets, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

Oxycodone HCl Controlled-Release Tablets may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of Oxycodone HCl Controlled-Release Tablets is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

Oxycodone HCl Controlled-Release Tablets should be used with caution and started in a reduced dosage (1/3 to 1/2 of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of Oxycodone HCl Controlled-Release Tablets.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Postoperative Use

Oxycodone HCl Controlled-Release Tablets are not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).

Oxycodone HCl Controlled-Release Tablets are not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) for patients not previously taking the drug, because its safety in this setting has not been established.

Oxycodone HCl Controlled-Release Tablets are not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.

Oxycodone HCl Controlled-Release Tablets are only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).

Patients who are already receiving Oxycodone HCl Controlled-Release Tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

Oxycodone HCl Controlled-Release Tablets and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued (see **DOSAGE AND ADMINISTRATION: Cessation of Therapy**).

Information for Patients/Caregivers

If clinically advisable, patients receiving Oxycodone HCl Controlled-Release Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that Oxycodone HCl Controlled-Release Tablets contain oxycodone, which is a morphine-like substance.

2. Patients should be advised that Oxycodone HCl Controlled-Release Tablets were designed to work properly only if swallowed whole. Oxycodone HCl Controlled-Release Tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.

3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

4. Patients should be advised not to adjust the dose of Oxycodone HCl Controlled-Release Tablets without consulting the prescribing professional.

5. Patients should be advised that Oxycodone HCl Controlled-Release Tablets may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).

6. Patients should not combine Oxycodone HCl Controlled-Release Tablets with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.

7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.

8. Patients should be advised that Oxycodone HCl Controlled-Release Tablets are a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.

9. Patients should be advised that they may pass empty matrix "ghosts" (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.

10. Patients should be advised that if they have been receiving treatment with Oxycodone HCl Controlled-Release Tablets for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the Oxycodone HCl Controlled-Release Tablets dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

11. Patients should be instructed to keep Oxycodone HCl Controlled-Release Tablets in a secure place out of the reach of children. When Oxycodone HCl Controlled-Release Tablets are no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction

Oxycodone HCl Controlled-Release Tablets are an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including Oxycodone HCl Controlled-Release Tablets, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part by cytochrome P450 2D6 and cytochrome P450 3A4 and in theory can be affected by other drugs.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as polycyclic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

Oxycodone HCl Controlled-Release Tablets, like all opioid analgesics, should be started at 1/3 to 1/2 of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/mL and with activation 48 hours after exposure at doses of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

Pregnancy

Teratogenic Effects - Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Oxycodone HCl Controlled-Release Tablets are not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving Oxycodone HCl Controlled-Release Tablets because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of Oxycodone HCl Controlled-Release Tablets have not been established in pediatric patients below the age of 18. **It must be remembered that Oxycodone HCl Controlled-Release Tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15% (see **PHARMACOKINETICS AND METABOLISM**). Of the total number of subjects (445) in clinical studies of Oxycodone HCl Controlled-Release Tablets, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received Oxycodone HCl Controlled-Release Tablets. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to 1/3 to 1/2 of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of Oxycodone HCl Controlled-Release Tablets in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at 1/3 to 1/2 the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

The safety of Oxycodone HCl Controlled-Release Tablets was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 187 patients received Oxycodone HCl Controlled-Release Tablets in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with Oxycodone HCl Controlled-Release Tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with Oxycodone HCl Controlled-Release Tablets are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cease or decrease in intensity as Oxycodone HCl Controlled-Release Tablet therapy is continued and some degree of tolerance is developed.

Clinical trials comparing Oxycodone HCl Controlled-Release Tablets with immediate-release oxycodone and placebo revealed a similar adverse event profile between Oxycodone HCl Controlled-Release Tablets and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

Table 3

	Oxycodone HCl Controlled-Release Tablets (n=227)	Immediate-Release (n=225)	Placebo (n=45)
	(%)	(%)	(%)
Constipation	(23)	(26)	(7)
Nausea	(23)	(27)	(11)
Somnolence	(23)	(24)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Vomiting	(12)	(14)	(7)
Headache	(7)	(8)	(7)
Dry Mouth	(6)	(7)	(2)
Asthenia	(6)	(7)	-
Sweating	(5)	(6)	(2)

The following adverse experiences were reported in Oxycodone HCl Controlled-Release Tablets-treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience.

Blood and lymphatic system disorders: lymphadenopathy

Cardiac disorders: palpitations (in the context of withdrawal)

Ear and labyrinth disorders: tinnitus

Endocrine disorders: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Eye disorders: abnormal vision

Gastrointestinal disorders: dysphagia, eructation, flatulence, gastrointestinal disorder, ileus, increased appetite, stomatitis

General disorders and administration site conditions: chest pain, edema, facial edema, malaise, pain, peripheral edema, thirst, withdrawal syndrome (with and without seizures)

Immune system disorders: anaphylactic or anaphylactoid reaction (symptoms of)

Infections and infestations: pharyngitis

Injury, poisoning and procedural complications: accidental injury

Investigations: hyponatremia, increased hepatic enzymes, ST depression

Metabolism and nutrition disorders: dehydration

Musculoskeletal and connective tissue disorders: neck pain

Nervous system disorders: abnormal gait, amnesia, hyperkinesia, hypertonia (muscular), hypesthesia, hypotonia, migraine, paresthesia, seizures, speech disorder, stupor, syncope, taste perversion, tremor, vertigo

Psychiatric disorders: agitation, depersonalization, depression, emotional lability, hallucination

Renal and urinary disorders: dysuria, hematuria, polyuria, urinary retention, urination impaired

Reproductive system and breast disorders: amenorrhea, decreased libido, impotence

Respiratory, thoracic and mediastinal disorders: cough increased, voice alteration

Skin and subcutaneous tissue disorders: dry skin, exfoliative dermatitis, urticaria

Vascular disorders: vasodilation

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of Oxycodone HCl Controlled-Release Tablets, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when Oxycodone HCl Controlled-Release Tablets are abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including Oxycodone HCl Controlled-Release Tablets, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

DOSAGE AND ADMINISTRATION

General Principles

OXYCODONE HCl CONTROLLED-RELEASE TABLETS ARE AN OPIOID AGONIST AND A SCHEDULE II CONTROLLED SUBSTANCE WITH AN ABUSE LIABILITY SIMILAR TO MORPHINE. OXYCODONE, LIKE MORPHINE AND OTHER OPIOIDS USED IN ANALGESIA, CAN BE ABUSED AND IS SUBJECT TO CRIMINAL DIVERSION.

OXYCODONE HCl CONTROLLED-RELEASE TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OXYCODONE HCl CONTROLLED-RELEASE TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

One Oxycodone HCl Controlled-Release 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets (see DOSAGE AND ADMINISTRATION).

Patients who are not currently taking opioid analgesics should generally be started on the lowest appropriate dose (see DOSAGE AND ADMINISTRATION; Initiation of Therapy).

In treating pain it is vital to assess the patient regularly and systematically. Therapy should also be regularly reviewed and adjusted based upon the patient's own reports of pain and side effects and the health professional's clinical judgment.

Oxycodone HCl Controlled-Release Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time. The controlled-release nature of the formulation allows Oxycodone HCl Controlled-Release Tablets to be effectively administered every 12 hours (see **CLINICAL PHARMACOLOGY; PHARMACOKINETICS AND METABOLISM**). While symmetric (same dose AM and PM), around-the-clock, q12h dosing is appropriate for the majority of patients, some patients may benefit from asymmetric (different dose given in AM than in PM) dosing, tailored to their pain pattern. It is usually appropriate to treat a patient with only one opioid for around-the-clock therapy.

Physicians should individualize treatment using a progressive plan of pain management such as outlined by the World Health Organization, the American Pain Society and the Federation of State Medical Boards Model Guidelines. Healthcare professionals should follow appropriate pain management principles of careful assessment and ongoing monitoring (see **BOXED WARNING**).

Initiation of Therapy

It is critical to initiate the dosing regimen for each patient individually, taking into account the patient's prior opioid and non-opioid analgesic treatment. Attention should be given to:

(1) the general condition and medical status of the patient;

(2) the daily dose, potency, and kind of the analgesic(s) the patient has been taking;

(3) the reliability of the conversion estimate used to calculate the dose of oxycodone;

(4) the patient's opioid exposure and opioid tolerance (if any);

(5) the **Special Instructions for Oxycodone HCl Controlled-Release 80 mg, and 160 mg Tablets, or a Single Dose Greater Than 40 mg;** and

(6) the balance between pain control and adverse experiences.

Care should be taken to use low initial doses of Oxycodone HCl Controlled-Release Tablets in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications (see **PRECAUTIONS: Drug-Drug Interactions**).

For initiation of Oxycodone HCl Controlled-Release Tablets therapy for patients previously taking opioids, the conversion ratios from Foley, KM. (NEJM, 1985; 313:84-95), found below, are a reasonable starting point, although not verified in well-controlled, multiple-dose trials.

Experience indicates a reasonable starting dose of Oxycodone HCl Controlled-Release Tablets for patients who are taking non-opioid analgesics and require continuous around-the-clock therapy for an extended period of time is 10 mg q12h. If a non-opioid analgesic is being provided, it may be continued. Oxycodone HCl Controlled-Release Tablets should be individually titrated to a dose that provides adequate analgesia and minimizes side effects.

1. Using standard conversion ratio estimates (see Table 4 below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral oxycodone.

2. When converting from oxycodone, divide the 24-hour oxycodone dose in half to obtain the twice a day (q12h) dose of Oxycodone HCl Controlled-Release Tablets.

3. Round down to a dose which is appropriate for the tablet strengths available (10 mg, 20 mg, 40 mg, and 80 mg tablets).

4. Discontinue all other around-the-clock opioid drugs when Oxycodone HCl Controlled-Release Tablet therapy is initiated.

5. No fixed conversion ratio is likely to be satisfactory in all patients, especially patients receiving large opioid doses. The recommended doses shown in Table 4 are only a starting point, and close observation and frequent titration are indicated until patients are stable on the new therapy.

Table 4

Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone*

	(Mg/Day Prior Opioid x Factor = Mg/Day Oral Oxycodone)	
	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	--
Codeine	0.15	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Methadone	1.5	3
Morphine	0.5	3

* **To be used only for conversion to oral oxycodone.** For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

In all cases, supplemental analgesia should be made available in the form of a suitable short-acting analgesic.

Oxycodone HCl Controlled-Release Tablets can be safely used concomitantly with usual doses of non-opioid analgesics and analgesic adjuvants, provided care is taken to select a proper initial dose (see **PRECAUTIONS**).

Conversion from Transdermal Fentanyl to Oxycodone HCl Controlled-Release Tablets

Eighteen hours following the removal of the transdermal fentanyl patch, Oxycodone HCl Controlled-Release Tablet treatment can be initiated. Although there has been no systematic assessment of such conversion, a conservative oxycodone dose, approximately 10 mg q12h of Oxycodone HCl Controlled-Release Tablets, should be initially substituted for each 25-µg/hr fentanyl transdermal patch. The patient should be followed closely for early titration, as there is very limited clinical experience with this conversion.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naive, will experience side effects. Frequently the side effects from Oxycodone HCl Controlled-Release Tablets are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with antiemetics or other modalities may relieve these symptoms and should be considered.

Patients receiving Oxycodone HCl Controlled-Release Tablets may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

Individualization of Dosage

Once therapy is initiated, pain relief and other opioid effects should be frequently assessed. Patients should be titrated to adequate effect (generally mild or no pain with the regular use of no more than two doses of supplemental analgesia per 24 hours). Patients who experience breakthrough pain may require dosage adjustment or rescue medication. Because steady-state plasma concentrations are approximated within 24 to 36 hours, dosage adjustment may be carried out every 1 to 2 days. It is most appropriate to increase the q12h dose, not the dosing frequency. There is no clinical information on dosing intervals shorter than q12h. As a guideline, except for the increase from 10 mg to 20 mg q12h, the total daily oxycodone dose usually can be increased by 25% to 50% of the current dose at each increase.

If signs of excessive opioid-related adverse experiences are observed, the next dose may be reduced. If this adjustment leads to inadequate analgesia, a supplemental dose of immediate-release oxycodone may be given. Alternatively, non-opioid analgesic adjuvants may be employed. Dose adjustments should be made to obtain an appropriate balance between pain relief and opioid-related adverse experiences.

If significant adverse events occur before the therapeutic goal of mild or no pain is achieved, the events should be treated aggressively. Once adverse events are under control, upward titration should continue to an acceptable level of pain control.

During periods of changing analgesic requirements, including initial titration, frequent contact is recommended between physician, other members of the healthcare team, the patient and the caregiver/family.

Special Instructions for Oxycodone HCl Controlled-Release 80 mg Tablets, or a single dose greater than 40 mg (for use in opioid-tolerant patients only.)

Oxycodone HCl Controlled-Release 80 mg Tablets, or a single dose greater than 40 mg, are for use only in opioid-tolerant patients only. A single daily dose greater than 40 mg, or total daily doses greater than 80 mg, may cause fatal respiratory depression when administered to patients who are not tolerant to the respiratory depressant effects of opioids. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

One Oxycodone HCl Controlled-Release 160 mg tablet is comparable to two 80 mg tablets when taken on an empty stomach. With a high-fat meal, however, there is a 25% greater peak plasma concentration following one 160 mg tablet. Dietary caution should be taken when patients are initially titrated to 160 mg tablets.

Supplemental Analgesia

Most patients given around-the-clock therapy with controlled-release opioids may need to have immediate-release medication available for exacerbations of pain or to prevent pain that occurs predictably during certain patient activities (incident pain).

Maintenance of Therapy

The intent of the titration period is to establish a patient-specific q12h dose that will maintain adequate analgesia with acceptable side effects for as long as pain relief is necessary. Should pain recur then the dose can be incrementally increased to re-establish pain control. The method of therapy adjustment outlined above should be employed to re-establish pain control.

During chronic therapy, especially for non-cancer pain syndromes, the continued need for around-the-clock opioid therapy should be reassessed periodically (e.g., every 6 to 12 months) as appropriate.

Cessation of Therapy

When the patient no longer requires therapy with Oxycodone HCl Controlled-Release Tablets, doses should be tapered gradually to prevent signs and symptoms of withdrawal in the physically dependent patient.

Conversion from Oxycodone HCl Controlled-Release Tablets to Parenteral Opioids

To avoid overdose, conservative dose conversion ratios should be followed.

SAFETY AND HANDLING

Oxycodone HCl Controlled-Release Tablets are solid dosage forms that contain oxycodone, which is a controlled substance. Like morphine, oxycodone is controlled under Schedule II of the Controlled Substances Act.

Oxycodone HCl Controlled-Release Tablets have been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

HOW SUPPLIED

Oxycodone HCl Controlled-Release Tablets 10 mg are round, unscored, white-colored, convex tablets imprinted with OC on one side and 10 on the other. They are supplied as follows:

NDC 52152-408-02: child-resistant closure, opaque plastic bottles of 100

Oxycodone HCl Controlled-Release Tablets 20 mg are round, unscored, pink-colored, convex tablets imprinted with OC on one side and 20 on the other. They are supplied as follows:

NDC 52152-409-02: child-resistant closure, opaque plastic bottles of 100

Oxycodone HCl Controlled-Release Tablets 40 mg are round, unscored, yellow-colored, convex tablets imprinted with OC on one side and 40 on the other. They are supplied as follows:

NDC 52152-410-02: child-resistant closure, opaque plastic bottles of 100

Oxycodone HCl Controlled-Release Tablets 80 mg are round, unscored, green-colored, convex tablets imprinted with OC on one side and 80 on the other. They are supplied as follows:

NDC 52152-411-02: child-resistant closure, opaque plastic bottles of 100

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container.

CAUTION
DEA Order Form Required.

Distributed by:
Actavis Totowa LLC
990 Riverview Drive
Totowa, NJ 07512 USA

U.S. Patent Numbers 5,508,042 and 7,129,248
8949-00 June 2009

PATIENT INFORMATION

OXYCODONE HCl CONTROLLED-RELEASE TABLETS CII

Oxycodone HCl Controlled-Release Tablets, 10 mg
Oxycodone HCl Controlled-Release Tablets, 20 mg
Oxycodone HCl Controlled-Release Tablets, 40 mg
Oxycodone HCl Controlled-Release Tablets, 80 mg

℞ Only

Read this information carefully before you take Oxycodone HCl Controlled-Release Tablets. Also read the information you get with your refills. There may be something new. This information does not take the place of talking with your doctor about your medical condition or your treatment. Only you and your doctor can decide if Oxycodone HCl Controlled-Release Tablets are right for you. Share the important information in this leaflet with members of your household.

What Is The Most Important Information I Should Know About Oxycodone HCl Controlled-Release Tablets?

- **Use Oxycodone HCl Controlled-Release Tablets the way your doctor tells you to.**
- **Use Oxycodone HCl Controlled-Release Tablets only for the condition for which it was prescribed.**
- **Oxycodone HCl Controlled-Release Tablets are not for occasional ("as needed") use.**
- **Swallow the tablets whole.** Do not break, crush, dissolve, or chew them before swallowing. Oxycodone HCl Controlled-Release Tablets work properly over 12 hours only when swallowed whole. **If a tablet is broken, crushed, dissolved, or chewed, the entire 12 hour dose will be absorbed into your body all at once. This can be dangerous, causing an overdose, and possibly death.**
- **Keep Oxycodone HCl Controlled-Release Tablets out of the reach of children.** Accidental overdose by a child is dangerous and may result in death.
- **Prevent theft and misuse.** Oxycodone HCl Controlled-Release Tablets contain a narcotic painkiller that can be a target for people who abuse prescription medicines. Therefore, keep your tablets in a secure place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is dangerous and against the law.

What are Oxycodone HCl Controlled-Release Tablets?

Oxycodone HCl Controlled-Release Tablets are tablets that come in several strengths and contain the medicine oxycodone (ox-e-KOE-done). This medicine is a painkiller like morphine. Oxycodone HCl Controlled-Release Tablets treat moderate to severe pain that is expected to last for an extended period of time. Use Oxycodone HCl Controlled-Release Tablets regularly during treatment. It contains enough medicine to last for up to twelve hours.

Who Should Not Take Oxycodone HCl Controlled-Release Tablets?

Do not take Oxycodone HCl Controlled-Release Tablets if
- your doctor did not prescribe Oxycodone HCl Controlled-Release Tablets for you.
- your pain is mild or will go away in a few days.
- your pain can be controlled by occasional use of other painkillers.
- you have severe asthma or severe lung problems.
- you have had a severe allergic reaction to codeine, hydrocodone, dihydrocodeine, or oxycodone (such as Tylox, Tylenol with Codeine, or Vicodin). A severe allergic reaction includes a severe rash, hives, breathing problems, or dizziness.
- you had surgery less than 12 - 24 hours ago and you were not taking Oxycodone HCl Controlled-Release Tablets just before surgery.

Your doctor should know about all your medical conditions before deciding if Oxycodone HCl Controlled-Release Tablets are right for you and what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury
- liver or kidney problems
- adrenal gland problems, such as Addison's disease
- convulsions or seizures
- alcoholism
- hallucinations or other severe mental problems
- past or present substance abuse or drug addiction

If any of these conditions apply to you, and you haven't told your doctor, then you should tell your doctor before taking Oxycodone HCl Controlled-Release Tablets.

If you are pregnant or plan to become pregnant, talk with your doctor. Oxycodone HCl Controlled-Release Tablets may not be right for you. **Tell your doctor if you are breast feeding.** Oxycodone HCl Controlled-Release Tablets will pass through the milk and may harm the baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious medical problems when taken with Oxycodone HCl Controlled-Release Tablets, especially if they cause drowsiness.

How Should I Take Oxycodone HCl Controlled-Release Tablets?

- **Follow your doctor's directions exactly.** Your doctor may change your dose based on your reactions to the medicine. Do not change your dose unless your doctor tells you to change it. Do not take Oxycodone HCl Controlled-Release Tablets more often than prescribed.
- **Swallow the tablets whole. Do not break, crush, dissolve, or chew before swallowing. If the tablets are not whole, your body will absorb too much medicine at one time. This can lead to serious problems, including overdose and death.**
- **If you miss a dose,** take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.
- **In case of overdose,** call your local emergency number or Poison Control Center right away.
- **Review your pain regularly with your doctor** to determine if you still need Oxycodone HCl Controlled-Release Tablets.
- **You may see tablets in your stools (bowel movements).** Do not be concerned. Your body has already absorbed the medicine.

If you continue to have pain or bothersome side effects, call your doctor

Stopping Oxycodone HCl Controlled-Release Tablets. Consult your doctor for instructions on how to stop this medicine slowly to avoid uncomfortable symptoms. You should not stop taking Oxycodone HCl Controlled-Release Tablets all at once if you have been taking it for more than a few days.

After you stop taking Oxycodone HCl Controlled-Release Tablets, flush the unused tablets down the toilet.

What Should I Avoid While Taking Oxycodone HCl Controlled-Release Tablets?

- **Do not drive, operate heavy machinery, or participate in any other possibly dangerous activities** until you know how you react to this medicine. Oxycodone HCl Controlled-Release Tablets can make you sleepy.
- **Do not drink alcohol while using Oxycodone HCl Controlled-Release Tablets. It may increase the chance of getting dangerous side effects.**
- **Do not take other medicines without your doctor's approval.** Other medicines include prescription and non-prescription medicines, vitamins, and supplements. Be especially careful about products that make you sleepy.

What are the Possible Side Effects of Oxycodone HCl Controlled-Release Tablets?

Call your doctor or get medical help right away if
- your breathing slows down
- you feel faint, dizzy, confused, or have any other unusual symptoms

Some of the common side effects of Oxycodone HCl Controlled-Release Tablets are nausea, vomiting, dizziness, drowsiness, constipation, itching, dry mouth, sweating, weakness, and headache. Some of these side effects may decrease with continued use.

There is a risk of abuse or addiction with narcotic painkillers. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while using Oxycodone HCl Controlled-Release Tablets.

These are not all the possible side effects of Oxycodone HCl Controlled-Release Tablets. For a complete list, ask your doctor or pharmacist.

General Advice About Oxycodone HCl Controlled-Release Tablets

- Do not use Oxycodone HCl Controlled-Release Tablets for conditions for which it was not prescribed.
- Do not give Oxycodone HCl Controlled-Release Tablets to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems, including death.

This leaflet summarizes the most important information about Oxycodone HCl Controlled-Release Tablets. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about Oxycodone HCl Controlled-Release Tablets that is written for health professionals.

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